(c) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes.

REMARKS

Claims 1-22 are currently pending. Applicant has amended the abstract to conform with the requirements of MPEP § 608.01(b). In addition, Applicant has amended claims 10-16, 21, and 22 to correct their improper multiple dependency and to further clarify the invention set forth in these claims. Applicant addresses below each of the current claim rejections according to its statutory basis.

Rejections Under 35 U.S.C. § 112, First Paragraph

The Office rejects claim 1 under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is allegedly not enabling. Specifically, the Office contends that the use of a label or solid support is critical to detecting the amount of the carrier-bound IgE-containing complexes. Claim 1 does not recite the use of a label. To clarify the invention of claim 1, Applicant has amended the claim to recite "detecting a label present in the carrier-bound IgE-containing complexes." Applicant notes that the label may be present in the complexes in different forms, as indicated in claims 2-6 and 17. Applicant asserts that claim 1, as amended, is enabled and as such requests withdrawal of this rejection.

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Claim 8 stands rejected under 35 U.S.C. § 112, first paragraph, as based on a disclosure which is allegedly not enabling. Specifically, the Office contends that since the label compound is bound to avidin, streptavidin or a functional derivative thereof, labeling a component of the assay with biotin is a critical element that is missing from the claim. To facilitate prosecution, Applicant has amended claim 8 to recite a "ligand [that] is bound to biotin or a functional derivative thereof." Applicant therefore requests withdrawal of the Office's rejection.

The Office rejects claims 1-20 under 35 U.S.C. § 112, first paragraph, as not described in the specification in such a way as to enable one of ordinary skill in the art to make or use the invention. Specifically, the Office notes that step (c) of claim 1 recites "a mixture II comprising carrier-bound IgE-containing complexes" and that step (d) recites "separating the carrier-bound IgE-containing complexes from the mixture II." Applicant notes that the language quoted by the Office is actually found in steps (b) and (c) of claim 1, respectively. According to the Office, mixture II contains no other components besides the carrier-bound IgE-containing complexes, thus separation is not enabled. Applicant respectfully traverses the Office's rejection of claims 1-20 on the following grounds.

Mixture II contains several components. As set forth in step (b) of claim 1, it is created by "mixing the mixture I with a carrier to which is bound (iii) an IgE receptor." For example, if the carrier is in particulate form, the resulting mixture II includes the unbound carrier-IgE receptor molecules, items from mixture I which include components of the liquid sample (i.e., other proteins if the liquid sample is a biological sample), unbound ligand, and the targeted carrier-bound IgE-containing complexes. Thus,

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contrary to the Office's reading of claim 1, mixture II does contain other components besides the targeted carrier-bound IgE-containing complexes. Accordingly, step (c) of claim 1 recites "separating the carrier-bound IgE-containing complexes from the mixture II." Applicant asserts that since there are other components present in mixture II besides carrier-bound IgE-containing complexes, the process of separating these complexes from these other components is enabled. Applicant requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 1-20 stand rejected as allegedly indefinite. Specifically the Office notes that the dependent claims of this rejection lack proper antecedent basis. Applicant has amended claims 2-6 and 17, changing them to independent form. Applicant has also amended claims 7-16, 18, and 19 to provide proper antecedent basis. Applicant asserts that these rejections are now moot.

The Office also notes that claim 1 does not specify IgE as an antigen or an antibody, does not indicate that the sample may contain IgE antibody, and does not indicate what the IgE complex is comprised of. Further, the Office notes that "mixture I" in line 8 and "IgE receptor" in line 9 lack antecedent support. Solely to clarify the claimed invention, Applicant has amended claim 1 to recite "[a] method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of: (a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

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(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor ...." By these amendments to claim 1, Applicant has now rendered the Office's rejection of claim 1 moot and requests that this rejection be withdrawn.

The Office also rejects claim 1 as allegedly indefinite because it contains the broad recitation of "IgE receptor" and the narrower recitation of "IgE receptor being CD23." To clarify the claimed invention, Applicant has amended claim 1 to recite "wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI." Thus, the term "IgE receptor" means CD23, FcεRI, or a mix of both.

Claim 1 is confusing to the Office because mixture II comprises carrier-bound IgE complexes and it is unclear how these complexes may be separated as in step (c). Applicant refers to the argument above regarding this claim. Specifically, mixture II contains more than just the targeted carrier-bound IgE complexes. Thus, step (c) speaks to isolating these complexes from the other components of mixture II. For example, such separation may be accomplished by magnetic separation, filtration, sedimentation, centrifugation, chromatography, or column chromatography. *See* the specification at page 11 lines 1-3.

The Office further notes that the term "mixture II" in claims 7 and 20 lack proper antecedent support and that claim 19 lacks a needed open parenthesis. Applicant has amended claims 7 and 20 to provide proper antecedent basis and claim 19 to provide the requested open parenthesis.

According to the Office, claim 17 is indefinite because the use of a detection system is not recited in any sequential order. Applicant has amended claim 17 to indicate that the claimed labeled anti-IgE antibody may be added during step (a) or step

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(b) or step (c) of the method. Applicant refers to the instant specification at page 9, lines 3-10, which indicates the different stages at which a labeled anti-IgE antibody may be added. Thus, claim 17 is not indefinite.

Claim 19 is confusing to the Office because it recites "carrier-bound complexes formed in step (c)." The Office notes the these complexes are formed in step (b). To clarify the claimed invention, Applicant has amended claim 19 to recite "wherein the label compound coupled to the antibody to the IgE to be detected is added to the carrier-bound complexes separated in step (c)." Thus, the labeled antibody is added once the carrier-bound complexes have been "separate[d] . . . from . . . mixture II."

Applicants contend that the above amendments and remarks have rendered the Office's rejection of claims 1-20 under 35 U.S.C. § 112, second paragraph, moot and respectfully request withdrawal of these rejections.

Rejection Under 35 U.S.C. § 101

Claims 21 and 22 stand rejected because the claims allegedly recite a use without setting forth any steps involved in the process. To facilitate prosecution, Applicant has amended claims 21 and 22 to recite the process steps. Applicant therefore respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 102

The Office rejects claims 1-14, 16, and 20 under 35 U.S.C. § 102(e) as allegedly anticipated by Johansen et al. (U.S. Patent 6,087,188; "Johansen"). Specifically, the Office asserts that Johansen teaches a method of detecting an antibody comprising the steps of mixing the ligand bound to biotin with an antibody directed to the antibody to be detected bound to paramagnetic particles, a chemiluminescent acridinium compound

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bound to avidin or streptavidin, and the sample containing the antibody to be detected. The Office further notes that Johansen teaches several other related embodiments of this method. Applicant respectfully traverses the Office's rejection.

Johansen does not teach every element of the claimed invention. Specifically, every embodiment taught by Johansen uses an anti-IgE antibody to capture the IgE bound to a ligand. The Office has acknowledged this in its rejection of the claims by indicating that "the ligand antigen, antibody or hapten bound to biotin with the sample; [and] an antibody . . . directed against the antibody to be detected" are mixed together according to Johansen's teaching. In contrast, the claimed invention uses an IgE receptor to capture the IgE antibody to be detected that is bound to a ligand. Johansen does not teach using an IgE receptor to bind IgE antibody/ligand complexes. As such, Johansen does not teach every element of the claimed invention and fails to satisfy the requirements for anticipation. Thus, Applicant respectfully requests that this rejection be withdrawn.

Claims 1 and 17-19 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Frank et al. (U.S. Patent 5,945,294; "Frank"). According to the Office, Frank teaches a method for detecting IgE comprising using FcεR as a capture molecule immobilized onto a substrate, wherein the sample is added and the resulting complex detected with an indicator molecule that binds to the complex. Applicant notes that Frank discloses several embodiments of assays to detect IgE in a sample, the majority of which call for the immobilization of a component onto a substrate. The embodiment most closely related to the present invention is Frank's lateral flow assay. See columns 13 and 14. In this assay, however, Frank used an antigen (ligand) that was fixed to a

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plastic bead. The instant invention uses a free, dissolved ligand. Thus, Frank does not disclose all of the claimed invention's elements and cannot anticipate claims 1 and 17-19. Applicant respectfully requests that the Office withdraw its rejection of these claims.

Rejection Under 35 U.S.C. § 103

The Office rejects claim 15 under 35 U.S.C. § 103(a) as allegedly unpatentable over Johansen in further view of Johnson et al. (U.S. Patent 6,034,066; "Johnson") and Frank et al. (U.S. Patent 6,060,326; "Frank 2"). According to the Office, it would have been obvious to one of ordinary skill in the art to use the IgE receptors of Johnson and Frank 2 to measure IgE according to the method of Johansen because CD23 and FcεR are specific to IgE antibodies. Applicant respectfully traverses the Office's rejection for the following reasons.

First, Johansen, as discussed above, does not teach the use of IgE receptors for capturing IgE antibody nor does it suggest the use of IgE receptors in a detection assay. Instead, this reference uses anti-IgE antibodies. Further, as the Office notes, Johansen does not teach a method of quantifying IgE by using CD23 alone to obtain a first measurement and then using FcεRI alone to obtain a second measurement. Second, Johnson discusses only CD23 and its relationship to IgE antibodies. Applicant notes that this reference does not teach FcεRI nor does it teach anything about IgE antibody detection assays. Thus, like Johansen, Johnson does not teach a method of quantifying IgE by using CD23 alone to obtain a first measurement and then using FcεRI alone to obtain a second measurement, as Johnson does not discuss FcεRI at all. Third, Frank 2 teaches the use of FcεRI only and does not teach CD23 (FcεRII). As such, Frank 2 also fails to teach a two part detection assay in which CD23 alone is used

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to obtain a first measurement and then FcεRI alone is used to obtain a second measurement. Applicant notes that claim 15 recites quantification "using both CD23 alone to obtain a first measurement and using FcεRI alone to obtain a second measurement." As discussed above, none of the three references relied upon by the Office, alone or in combination, teach the concept of a detection assay that uses two different molecules to obtain two different measurements let alone the specific concept of using CD23 as a first molecule and FcεRI as a second molecule.

In addition, Applicant asserts that none of the three references cited by the Office contain a motivation to combine their teachings in such a way as to develop the invention of claim 15. Applicant sought to design an IgE antibody detection assay that closely simulates the *in vivo* interactions of IgE antibodies with their ligands and their receptors. To this end, Applicant has developed a detection assay that 1) uses an IgE receptor as a capture agent; 2) carries out the binding of the ligand to the target IgE antibody before or at the same time the antibody binds to an IgE receptor; 3) uses a dissolved ligand; and 4) allows binding to take place in the presence of interfering substances that may be present in the sample that contains the target IgE antibody. Neither Johansen, Johnson, nor Frank 2 provide any motivation for producing an IgE antibody detection assay with these features.

For these reasons, Applicant contends that claim 15 is not unpatentable over Johansen in further view of Johnson and Frank 2. Applicant therefore respectfully requests that the Office withdraw its rejection of this claim.

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Conclusion

In view of the foregoing amendments and remarks, Applicant respectfully requests the reconsideration and reexamination of this application and the timely allowance of pending claims 1-22.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: November 30, 2001

By: _____
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Application Number: 09/467,901
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Attorney Docket Number: 2405.0190-00

APPENDIX TO AMENDMENT OF NOVEMBER 30, 2001

Version with Markings to Show Changes Made

Amendments to the Claims

1. A method of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor [being] is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes.

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2. A method [according to claim 1, wherein the ligand is labeled] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved labeled ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

3. A method [according to claim 1, wherein the ligand used in step a) is bound to (iv) a label compound] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

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(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten, wherein the ligand is bound to a label compound, to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

4. A method [according to claim 1, wherein (iv) a label compound is added in step (a) in addition to (i) the sample and (ii) the ligand] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten and with (iii) a label compound to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

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(b) mixing the mixture I with a carrier to which is bound (iv) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II, and

(d) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

5. A method [according to claim 1, wherein a label compound is added to the carrier-bound IgE-containing complexes formed in step (b)] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) adding a label compound to the carrier-bound IgE-containing complexes formed in step (b),

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(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

6. A method [according to claim 1, wherein (iv) a label compound is added to the carrier-bound IgE-containing complexes resulting from the separation step (c) to form a mixture II'] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(c) separating the carrier-bound IgE-containing complexes from the mixture II,

(d) adding a label compound to the carrier-bound IgE-containing complexes resulting from the separation step (c) to form a mixture II', and

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(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

7. [A] The method according to claim 6, wherein the labeled and carrier-bound IgE-containing complexes are separated from the mixture II' and washed prior to step [(d)] (e).

8. [A] The method according to any one of claims 3-7, wherein [(iv)] the label compound is a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof and the ligand is bound to biotin or a functional derivative thereof.

9. [A] The method according to claim 8, wherein the chemiluminescent compound is an acridinium compound.

10. [A] The method according to [any of the preceding claims] claim 1, wherein the ligand is bound to biotin or a functional derivative thereof.

11. [A] The method according to [any of the preceding claims] claim 1, wherein the IgE-containing sample is contacted with the ligand and allowed to incubate to form a mixture I (step (a)) before contacting mixture I with the carrier/IgE receptor (step (b)).

12. [A] The method according to [any of claims 1-10] claim 1, wherein step (a) and (b) are carried out simultaneously in one operation.

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13. [A] The method according to [any of the preceding claims] claim 1, wherein the carrier is a particulate material.

14. [A] The method according to claim [13] 1, wherein the carrier is a paramagnetic particulate material.

15. [A] The method according to [any of the preceding claims] claim 1, wherein the IgE to be detected is quantified using both CD23 alone to obtain a first measurement and using FcεRI alone to obtain a second measurement.

16. [A] The method according to [any of the preceding claims] claim 1, wherein the number of ligand molecules is between 100% and 200% of the number of IgE molecules to be detected.

17. A method [according to claim 1 comprising using a detection system in the form of a label compound coupled to an antibody to the IgE to be detected] of detecting and/or quantifying an IgE antibody specific to a ligand in the form of an antigen, an antibody, or a hapten in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten, to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

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(c) separating the carrier-bound IgE-containing complexes from the mixture II,

(d) adding a label compound coupled to an antibody to the IgE to be detected to the complexes present in steps (a), (b), or (c) above, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting the label present in the carrier-bound IgE-containing complexes.

18. [A] The method according to claim 17, wherein the label compound is coupled to the antibody via biotin.

19. [A] The method according to claim 17 or 18, wherein the [detection system] label compound coupled to the antibody to the IgE to be detected is added to the carrier-bound complexes [formed] separated in step (c).

20. A method of detecting and/or quantifying a specific IgE antibody in a liquid sample suspected to contain the IgE antibody comprising the steps of:

(a) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes), wherein the ligand is bound to biotin or a functional derivative thereof,

(b) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor [being] is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

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(b') separating the carrier-bound IgE-containing complexes from the mixture II and washing said complexes,

(b") adding to the washed carrier-bound IgE-containing complexes a solution of (iv) a chemiluminescent compound covalently bound to avidin, streptavidin, or a functional derivative thereof to form a mixture II',

(c) separating the carrier-bound IgE-containing complexes from the mixture II' and washing the [said] complexes, and

(d) initiating a chemiluminescent reaction in the resulting IgE-containing complexes and detecting/measuring the resulting chemiluminescence, if any.

21. [Use of the method of any of claims 1-17 to monitor and evaluate] A method of monitoring and evaluating the immunological status of a subject comprising the steps of:

(a) obtaining a liquid sample suspected to contain an IgE antibody from the subject,

(b) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

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(c) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes.

22. [Use of the method of any of claims 1-17 to monitor and evaluate] A method of monitoring and evaluating the immunological status of a subject receiving Specific Allergy Vaccination (SAV) treatment comprising the steps of:

(a) obtaining a liquid sample suspected to contain an IgE antibody from the subject,

(b) contacting (i) the sample with (ii) a free dissolved ligand in the form of an antigen, an antibody, or a hapten to form a mixture I comprising complexes that comprise the IgE antibody and the ligand (IgE-containing complexes),

(c) mixing the mixture I with a carrier to which is bound (iii) an IgE receptor, wherein said IgE receptor is CD23 (FcεRII) and/or FcεRI, to form a mixture II comprising carrier-bound IgE-containing complexes,

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(d) separating the carrier-bound IgE-containing complexes from the mixture II, and

(e) determining the amount of the carrier-bound IgE-containing complexes formed by detecting a label present in the carrier-bound IgE-containing complexes.

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